Citation:

Albert CM, Oh K, Whang W, Manson JE, Chae CU, Stampfer MJ, Willett WC, Hu FB. Dietary alpha-linolenic acid intake and risk of sudden cardiac death and coronary heart disease. *Circulation.* 2005 Nov 22;112(21):3232-8.

PubMed ID: 16301356

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

The study examined the relationship of alpha-linolenic acid (ALA) intake to the risk of sudden cardiac death (SCD) and included associations for other coronary death and nonfatal MI during 18 years of follow-up.

Inclusion Criteria:

- Participant of the Nurses' Health Study
- 30-55 years of age
- Returned the 1984 questionnaire, which included food items critical for assessment of ALA intake
- Informed consent was obtained

Exclusion Criteria:

- Those who did not complete the dietary questionnaire and those with more than 10 blank items or implausible reported food intakes
- Those with a history of cancer

Description of Study Protocol:

Recruitment:

The Nurses' Health Study began in 1976 when 121,701 registered nurses completed a questionnaire about their medical history, cardiovascular risk factors, menopausal status, and lifestyle factors. This article did not describe how the nurses were selected for the Nurse's Health Study (published previously).

Design: Prospective cohort study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- Age-adjusted means or proportions of cardiovascular risk factors were computed across quintiles of ALA intake.
- Person-months of follow-up were calculated from the return date of the 1984 questionnaire to the date of the first end point, death, or 6/1/2002.
- The most recent dietary intake was used and the last observation was carried forward for those with missing values.
- Proportional-hazards models were used to compute age- and multivariate-adjusted ratios as estimates of relative risk across quintiles of ALA. Multivariate model 1 controlled for coronary risk factors, prior report of CVD, alcohol and aspirin intake, vitamin supplements, and postmenopausal hormone use.
- Model 2 included Model 1 covariates and intake of other fatty acids.
- To determine if effect of ALA might differ in secondary or primary prevention, similar analyses were performed after stratifying the population by the presence of absence of a confirmed cardiovascular event.

Data Collection Summary:

Timing of Measurements

- Questionnaires including the food frequency questionnaire were completed in 1984, 1986, 1990, 1994 and 1998.
- Outcomes recorded as occurring after the questionnaire completion in 1984 and before this study data collection was completed in 6/02.

Dependent Variables

- Study end points included incident cases of CD (death occurring within 1 hour of symptom onset), other fatal CHAD and nonfatal MI that occurred after return of the 1984 questionnaire and before 6/1/2002.
- Participants or family members gave permission for medical records to be obtained.
- Medical records were reviewed by physicians blinded to exposure status, to confirm MI diagnosis.
- If no medical record was available, but confirmation was obtained by interview or letter, the participants were included (20%).
- Deaths were confirmed by death certificate, medical record, or family interview.

Independent Variables

- Intake of ALA measured by semiquantitative food frequency questionnaire
- The USDA nutrient composition database was used to analyze intake of ALA.

Control Variables

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- Long-chain n-3 fatty acid intake
- Coronary risk factors
- Prior report of CVD
- Alcohol and aspirin intake
- Vitamin supplements
- Postmenopausal hormone use

Description of Actual Data Sample:

Initial N: 97,423 women returned the baseline 1984 questionnaire

Attrition (final N): 76,763 women

Age: aged 30 - 55 years in 1976. Mean ages across ALA quintiles were 50.7 to 51.3 years.

Ethnicity: Not described in this study.

Other relevant demographics

Anthropometrics

Location: United States

Summary of Results:

Key Findings

- During 18 years of follow-up, 206 cases of SCD, 641 other CHD deaths, and 1604 nonfatal MIs were identified.
- ALA was the predominant n-3 fatty acid consumed, intake ranging from 0.37% of total energy intake to 0.74%.
- Women who consumed more ALA were older, more likely to be obese, have a history of diabetes, drink light to moderate amounts of alcohol and smoke cigarettes. They were less likely to have a history of CVD, drink larger amounts of alcohol, and use aspirin or multivitamins on a regular basis.
- In age-adjusted analysis, greater ALA intake was associated with a trend toward a lower risk of SCD (P for trend Multivariate I and II were both 0.02).
- Women in the 2 highest quintiles of ALA intake had a 38-40% lower SCD risk (every 0.1% increase in energy intake from ALA was associated with a 12% reduction in SCD risk).
- This inverse relation with SCD risk was linear and remained significant even among women with high intakes of long-chain n-3 fatty acids.
- ALA intake was not significantly related to other (nonsudden) fatal CHD events or to nonfatal MI.

Relative Risks (95% Confidence Interval) of SCD by Quintiles of Linolenic Fatty Acid Intake

Median (% Energy)	1 (0.37)	2 (0.45)	3 (0.52)	4 (0.60)	5 (0.74)	P for Trend
No. Cases	54	44	40	32	36	
Multivariate I	1	0.85 (0.60-1.33)	0.76 (0.50-1.16)	0.63 (0.40-0.98)	0.63 (0.41-0.98)	0.02
Multivariate II	1	0.86 (0.57-1.29)	0.76 (0.50-1.16)	0.62 (0.39-0.98)	0.60 (0.37-0.96)	0.02

Author Conclusion:

In conclusion, these prospective data provide evidence for an inverse association between ALA intake and SCD risk among women. Because the majority of women who die suddenly do not have a history of CVD and few cardiac arrests survive to hospital discharge, any substantial reduction in SCD will require prevention efforts in the general population as well as in those with a history of CVD. If diets and/or supplements enriched with ALA were found to have antiarrhythmic properties or to reduce the risk of SCD in randomized trials, the public health impact of such a low-cost and easily accessible intervention could be significant.

Reviewer Comments:

18 year follow-up, diet measured multiple times. Limitations included that this is an observational study which cannot prove causality; information on coronary risk factors and diet were ascertained by self-report; and the selective nature of the cohort (US female registered nurses) may limit generalizability.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes

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1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	No
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes

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	7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
	7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
	7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes

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